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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,146	05/26/2006	Alexander A. Khromykh	45930.5.1	9049

22859 7590 06/23/2008

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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
06/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,146	KHROMYKH, ALEXANDER A.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/5/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received May 19, 2008.

Election/Restrictions

Applicant's election with traverse of group I, claims 1-26 and the species of Kunjin virus replicon is acknowledged. Applicant argues that Examiner misidentified the special technical feature of the present invention. Applicant states that the special technical feature of the present invention is the single translation product comprising C, prM and E structural proteins. In response, a reference cited in Applicant's IDS of 12/5/2005 by Khromykh (WO/03/046189 A1) teach the single expression product of flavivirus C, prM and E structural proteins as discussed in the art rejection below. Thus because Khromykh teaches the special technical feature of the present invention, Applicant's invention does not contribute special technical feature when viewed over the prior art. Therefore the present claims lack Unity of Invention and thus restriction is set forth as it applies to U.S. practice.

Upon further consideration claims 27 and 28 of group II have been rejoined. New claims 35-37, drawn to methods of producing a recombinant protein in a host cell are currently under examination. Upon rejoinder of claims 27, 28 and new claims 35-37 the restriction requirement is set forth as follows:

Group I, claims 1-28 and 35-37, drawn to a flaviviral packaging construct, methods of producing flavivirus VLP and a method of producing a recombinant protein.

Group II, claims 29-34, drawn to a method of immunizing an animal.

Restriction requirement is deemed proper and is made FINAL. Claims 29-34 and 32-34 are withdrawn because they are drawn to non-elected invention.

Claims 1-28 and 35-37 are under examination in this Office Action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/5/2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-10, 12-28, and 35-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: **a)** Kunjin packaging construct/replicon and a Kunjin VLPs expressing C, prM, and E genes (tetKUNCprME), **b)** the methods of producing Kunjin flavivirus VLPs, **c)** the methods of producing a recombinant protein from Kunjin VLPs, **d)** mutations i-iv listed in claim 15, and **e)** the immunogenic composition comprising Kunjin virus VLPs does not reasonably provide enablement for packaging construct/replicon of any flavivirus origin and the above methods involving production of any flavivirus VLPs, any mutation of the VLP construct, or a vaccine or a immunotherapeutic composition for neither Kunjin or any other flavivirus.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Unpredictability of the art. The art in the area of flavivirus expression vectors is unpredictable. The flavivirus group of viruses is comprised of a large number of poorly characterized viruses, most of which have not been genetically manipulated with regard to generation of recombinant expression systems. While the flaviviruses share some common features with regard to genome organization, they share little sequence homology. The packaging mechanisms for flavivirus RNA were unknown at the time of applicants' invention. Many flaviviral proteins can be cytotoxic to cells and the skilled artisan would need to develop cell lines which could support replication of flavivirus replicons and the viral protein(s) necessary to complement *in trans* the deleted flaviviral structural proteins. This would involve essentially trial and error experimentation.

2) State of the art. The state of the art with regard to the generation of recombinant flavivirus expression vectors and replicons is poorly developed. Development of flavivirus

expression systems and replicons requires a detailed understanding of the molecular biology of the viruses, the packaging mechanisms by which the flavivirus genomes are encapsidated in particles, the sequences which can be provided *in trans* vs. those that need to be provided *in cis*, etc. A prerequisite for beginning to understand the molecular biology of flaviviruses is the generation of a stable full length cDNA copy of a flavivirus RNA capable of producing an infectious RNA transcript *in vitro*. However, most flavivirus full length cDNA clones were not generated until after the effective filing date of the instant invention (See for example, Bredenbeek et al., J. Gen. Virol., 2003, Vol. 84 (Pt. 5), pp. 1261-1268; Yamshchikov et al., Virology, 2001, Vol.. 281(2), pp. 294-304). The claims also read on packaging any given flavivirus replicon by a vector encoding flavivirus packaging proteins from any other flavivirus. Neither applicants nor the prior art teaches encapsidation of a flavivirus replicon or any replicative flavivirus construct from one viral species (i.e. Dengue virus, West Nile Virus, HCV, etc.) by packaging components (i.e. structural proteins) from another flavivirus (i.e. tick borne encephalitis virus, yellow fever virus, etc.).

3) Number of working examples. Applicants present working examples only using the Kunjin virus (Figures 1-8 and Examples).

4) Scope of the claims. Claims are broadly drawn to a packaging construct of **any flavivirus** structural protein, a vaccine and an immunotherapeutic comprising any flavivirus replicon. The claims are drawn to a VLP comprising **any mutation** in non-structural proteins, a **vaccine and an immunotherapeutic**. The claims are rejected because the present specification does not provide an adequate enablement to practice the full scope of the present claims. The claims are rejected because the specification does not provide an adequate enablement for the

claimed vaccine or an immunotherapeutic. It is noted that the specification does not provide an adequate enablement for a vaccine or an immunotherapeutic even if the claims were limited to a Kunjin virus replicon.

It is noted that the recitation of specific structural proteins in claim 1, C, prM and E protein does not limit the claim to any specific flavivirus, because C, prM and E proteins are present in all flaviviruses (see Lobigs et al. Immunology and Cell Biology, 2004, Vol. 82, p. 184-188).

5) Amount of guidance provided by applicants. Applicants provided guidance only on the generation of Kunjin viral replicons expressing C, prM, and E genes (tetKUNCprME), vectors capable of expressing Kunjin viral structural proteins in the context of cell lines which persistently express said structural proteins and Kunjin viral replicons capable of expressing heterologous sequences. No guidance is provided on the generation of any other flavivirus replicons, packaging vectors or cell lines which persistently express any other flavivirus structural proteins. Applicants provide guidance with regard to making a Leucine residue 250 substituted by Proline in the NS 1 nonstructural protein, (ii) Alanine 30 substituted by Proline in the nonstructural protein NS2A; (iii) Asparagine 101 substituted by Aspartate in the nonstructural protein NS2A; and (iv) Proline 270 substituted by Serine in the nonstructural protein NS5. Making other random mutations within the non-structural proteins of Kunjin flavivirus or any other flavivirus would have had unpredictable results.

6) Nature of the invention. The invention involves a complex area of molecular biology; the generation of recombinant flaviviral gene expression and delivery systems. The invention

also reads on a flaviviral replicon which is encapsidated in proteins which are not native to the virus sequences being encapsidated.

7) Level of skill in the art. The level of skill in the art is high; however, given the unpredictability of the art, the lack of sufficient working examples, the poorly developed state of the art and the lack of guidance provided by applicants, it must be considered that the skilled artisan would have had to have conducted essentially trial and error experimentation in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

The term "vaccine" or an "immunotherapeutic" recited in the present claims by definition implies any preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others contracting the disease.

The specification contemplates generation of protective vaccines against viral infections and cancer ([0121], [0165], [0172], [0177]). The specification does not provide working examples showing vaccination and challenge of animals with infectious viruses. The skilled artisan would be therefore required to conduct an undue amount of experimentation in order to generate flaviviral constructs effective in induction of human specific and protective immune responses. It is noted that the claims are broadly drawn to any vaccines. In case of for example Dengue virus, HIV, or HCV, there is no effective vaccine available on the market. Moreover, as of today an effective vaccine based on viral particles encoding immunogenic genes is not available.

Due to the large quantity of experimentation necessary to generate the vaccine recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification in light of the high degree of unpredictability in the art regarding difficulties in generation of a protective vaccine, the absence of working examples directed to same, the complex nature of the invention, an undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-28 and 35-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Khromykh (WO/03/046189A1 in IDS of 12/15/2005).

Claims are drawn to a packaging construct for expression of flavivirus structural proteins in an animal cell. The construct comprises a promoter operably linked to a nucleotide encoding a flavivirus structural protein translation product that comprises that comprises C protein, prM protein and E protein. The promoter is a tetracycline repressible CMV promoter. The construct further comprises an IRESNeo selection marker. The flavivirus replicon is a Kunjin virus and the C, prM, and E proteins are structural proteins of a Kunjin virus. A packaging cell is a BHK21 cell. The construct further comprises a heterologous nucleic acid. The structural proteins of the replicon are mutated as follows: Leucine residue 250 substituted by Proline in the NS 1 nonstructural protein, (ii) Alanine 30 substituted by Proline in the nonstructural protein NS2A; (iii) Asparagine 101 substituted by Aspartate in the nonstructural protein NS2A; and (iv) Proline 270 substituted by Serine in the nonstructural protein NS5. The flaviviral construct is in RNA form. Claims are drawn to methods of producing flavivirus VLPs and producing a recombinant protein by infecting a host cell with the flaviviral replicon, producing VLPs and infecting a second host cell. The claims are drawn to compositions and a vaccine comprising the flavivirus VLPs.

Khromykh discloses Kunjin virus VLPs encoding and expressing a protein translation product comprising C protein, prM protein and E protein (see claims 1-5, 10-16, 24, and 25, Figures 10 and 11, Table 5, page 12, lines 24-29, page 14, lines 19-23, page 34, lines 19-25). The Kunjin virus VLP disclosed by Khromykh is in RNA form and encodes a heterologous nucleic acid encoding murine epitopes (see page 5, lines 25-30, page 10, lines 10-20, Figures 2 and 3).

The flaviviral packaging system disclosed by Khromykh comprises mutations in nonstructural proteins: Leucine residue 250 substituted by Proline in the NS 1 nonstructural

protein, (ii) Alanine 30 substituted by Proline in the nonstructural protein NS2A; (iii) Asparagine 101 substituted by Aspartate in the nonstructural protein NS2A; and (iv) Proline 270 substituted by Serine in the nonstructural protein NS5 (see claim 4, page 5, lines 1-15 and page 16, lines 1-10).

The flaviviral packaging system disclosed by Khromykh comprises a tetracycline repressible CMV promoter and the IRESNeo selection marker (see page 18, lines 10-15 and page 32, lines 30-31 and Figure 9). Khromykh discloses the BHK21 host cell (see page 18, lines 23-29, and Examples 1 and 4).

Khromykh discloses an immunogenic composition comprising flavivirus VLP encoding C protein, prM protein and E protein and a heterologous protein (see claims 36-50). It is noted that the claims are rejected for the enabled embodiment of the immunogenic composition.

Khromykh discloses methods of producing flavivirus VLPs and methods of producing a recombinant protein by infecting a host cell with the flaviviral replicon, producing VLPs and infecting a second host cell (see Example 1 and Results on pages 29-32).

Thus by this disclosure Khromykh anticipate the present claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-26 and are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No 6,893,866 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the present claims and claim 1 of the U.S. Patent No 6,893,866 B1 are drawn to an expression vector incapable of producing infectious virus comprising a nucleotide sequence encoding a flavivirus replicon derived from the Kunjin virus, the expression vector comprising the insertion site for heterologous nucleic acid, the expression vector comprising a heterologous nucleic acid, and further comprising a second expression construct that facilitates packaging of the expression construct into flavivirus like particles (VLPs).

Claims 1-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 66-79 of copending Application No. 11/098,283. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present and the copending Application are drawn to a flavivirus gene expression construct expressing Kunjin virus structural proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 5, 7-10, 12-32, of copending Application No. 11/816,350. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present and the copending Application are drawn to a flavivirus gene expression construct expressing Kunjin virus structural proteins.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen, Ph.D./

Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648